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Intense training overcomes effects of the val⁶⁶met BDNF polymorphism on short-term plasticity

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Abstract The val⁶⁶met polymorphism in the brain-derived neurotrophic factor (BDNF) gene impacts activity-dependent secretion of BDNF and modifies short-term cortical plasticity. The current study examined whether sustained training overcomes polymorphism effects on short-term plasticity and also examined polymorphism effects on long-term plasticity. Twenty-four subjects completed a 12-day protocol of daily training on a marble navigation task that required intense use of the first dorsal interosseus (FDI) muscle. In parallel, transcranial magnetic stimulation (TMS) mapping was used to assess serial measures of short-term cortical motor map plasticity, plus long-term cortical motor map plasticity, of the cortical FDI map. On Day 1, subjects with the polymorphism did not show significant short-term cortical motor map plasticity over 30 min of FDI activity, but subjects without the polymorphism did. After 5 days of intense training, a genotype-based difference in short-term cortical motor map plasticity was no longer found, as both groups showed short-term plasticity across the 30 min of FDI activity. Also, across 12 days of training, map area decreased significantly, in a manner that did not vary in relation to

genotype. Training of sufficient intensity and duration overcomes effects that the val⁶⁶met polymorphism has on short-term cortical motor map plasticity. The polymorphism-related differences seen with short-term plasticity are not found with long-term cortical motor map plasticity.

Keywords BDNF · Plasticity · Polymorphism · Training · Transcranial magnetic stimulation

Introduction

Brain-derived neurotrophic factor is abundantly found throughout the brain and is important for synaptic plasticity in normal brain function (Kang and Schuman 1995). In addition, changes in BDNF expression play a significant role in a number of neurological conditions (Gines et al. 2006; Zuccato and Cattaneo 2009). Increased BDNF signaling has been associated with improved outcome following stroke (Chen et al. 2005; Wu 2005). Such findings attest to the potential clinical and therapeutic implications of changes in brain BDNF signaling.

An opportunity to study changes in the human BDNF system arises in the context of a single nucleotide polymorphism at codon 66 of the BDNF gene (val⁶⁶met), which is common (Shimizu et al. 2004) and associated with reduced activity-dependent BDNF release (Egan et al. 2003). Presence of this val⁶⁶met polymorphism has been associated with numerous effects on the brain, including differences in cortical morphology (Pezawas et al. 2004), hippocampal function and synaptic plasticity (Egan et al. 2003), and episodic memory (Egan et al. 2003; Ho et al. 2006). An observation important to this investigation is that this polymorphism has also been associated with reduced short-term plasticity in motor cortex (Kleim et al. 2006;

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Cheeran et al. 2008; McHughen et al. 2010) and throughout the brain (McHughen et al. 2010).

These findings raise the question as to whether experience, such as with sustained training, can overcome these polymorphism effects on short-term plasticity. Prior studies suggest that this might be true, as days of exercise significantly increase brain BDNF levels (Neeper et al. 1995; Gomez-Pinilla et al. 2002) and amplify downstream BDNF effects (Berchtold et al. 2010). The primary aim of this study was to determine whether sustained training overcomes polymorphism effects on short-term plasticity. Short-term plasticity was probed using transcranial magnetic stimulation (TMS). This method measures the area of motor cortex from which a motor evoked potential can be elicited and also finds the most excitable spot in motor cortex and measures corticospinal output upon its stimulation. Measures of short-term plasticity are derived from examining the change in motor map area, as well as the change in corticospinal output, across a brief behavioral probe, i.e., one with a duration measured in minutes.

A secondary aim of this study was to understand the effects of the val⁶⁶met BDNF polymorphism on longer-term forms of plasticity, i.e., over time periods measured in days rather than minutes, a consideration that arises given that short-term and long-term forms of cortical plasticity arise on the basis of different neuronal mechanisms (Karni et al. 1995; Costa et al. 2004; Floyer-Lea and Matthews 2005). Long-term plasticity was also examined using TMS, derived by examining the change in motor map area and in corticospinal output across a longer behavioral probe, i.e., one with a duration measured in days. An improved understanding of polymorphism effects on long-term forms of brain plasticity is of considerable clinical relevance.

Materials and methods

Protocol overview

Study participation consisted of a baseline screening visit that included motor assessments and a buccal swab for genotyping, followed by 12 days of skilled motor training on a marble navigation task (MNT). On Days 1, 5, and 12 of training, subjects underwent TMS mapping of the brain motor system both before and after 30 min simple FDI activity, using a protocol described previously (Kleim et al. 2006, 2007). In this study, *short-term plasticity* was induced by 30 min of simple FDI activity, was defined as the change in the size of the cortical map for the FDI as determined via serial TMS over these 30 min, and was measured three times (on Days 1, 5, and 12). *Long-term plasticity* was induced by 12 days of MNT training, was defined as the change in TMS map area over these 12 days, and was measured from Day 1 to Day 12.

Subjects

A total of 24 healthy young subjects (12 with Val/Val genotype, referred to as Val/Val; and 12 with either one [$n = 11$] or two [$n = 1$] copies of the Met allele, referred to as Met carriers) provided written informed consent using procedures approved by the Institutional Review Board. Entry criteria included right handed, no neurological or psychiatric diagnoses, and no contraindication to TMS (Kleim et al. 2007). Forty subjects were screened, yielding 12 Met carriers who were offered study admission and accepted, and 28 Val/Val subjects, of whom the first 12 were offered study admission and accepted.

Genotyping

Determination of BDNF genotype was conducted as described elsewhere (McHughen et al. 2010).

Behavioral assessments

Subjects completed a medical history questionnaire, modified version of the Edinburgh Handedness Scale, Center for Epidemiologic Studies Depression Scale (CES-D), State-Trait Anxiety Inventory (STAI) questionnaires, and Wechsler digit span forward and backward. All subjects were then tested on three tests of fine motor skill, on the right side: maximum index finger tapping speed, time to complete the nine-hole pegboard, and maximum force of lateral pinch grip strength. Next, subjects were tested on reaction time using a computer keyboard response mechanism and in-house software.

TMS set-up

On Days 1, 5, and 12, subjects underwent a TMS study that included mapping before and after 30 min of FDI activity, as described elsewhere (Kleim et al. 2006, 2007) and summarized below.

Baseline TMS

Surface electromyography leads were recorded from right FDI (gain = 10,000 \times , bandpass filters 30–1,000 Hz). TMS used a Magstim 200² stimulator and 70-mm figure-of-eight stimulation coil (Magstim; Whitland, UK). To maximize consistency of coil placement, a high-resolution volumetric anatomical MRI scan template was registered to each subject usingBrainsight stereotactic software (Rogue Research; Montreal, QC). A 1-cm² grid was superimposed on the digital image of the cortical surface in order to guide stimulation sites. The site of lowest motor threshold (SOLMT), defined as the site which requires the least

amount of intensity to produce a motor evoked potential (MEP) ≥ 50 μ V in at least six of 10 pulses (Rossini et al. 1994) in the left hemisphere for the area controlling right FDI, was determined. Once the lowest motor threshold (LMT) and its respective SOLMT were determined, the SOLMT was probed by delivering 10 pulses at each of four intensity levels (90, 110, 130, and 150% LMT) in a pseudorandomized order. Following this, stimulation was applied systematically at 110% LMT in 1-cm increments across the cortical surface in a spiral pattern surrounding the SOLMT. Positive sites, defined as sites which, when stimulated at 110% LMT, produced an MEP ≥ 50 μ V in at least six of ten pulses, were noted. Sites which could not produce ≥ 50 μ V in at least six of 10 pulses were called “negative” sites, and the mapping procedure was repeated until all the positive sites were surrounded by negative sites, thus generating a motor map of cortical responses for FDI.

Short-term training paradigm

Immediately following baseline TMS, subjects completed 30 min of simple activity targeting the right FDI muscle, consisting of rapid FDI movements and forceful FDI movements.

Post-activity TMS

Immediately following the 30 min of FDI activity, TMS was again used to deliver 10 pulses at each of the four above levels of stimulation, and the mapping procedure was also repeated.

Marble navigation task

The MNT required subjects to navigate a marble through a sequence of target wells using their right index finger (Fig. 1), a task designed to make intensive demands on the FDI muscle during motor learning. Subjects were seated in front of a board containing nine shallow (1 mm deep) wells, arranged in a 3×3 grid. The right index finger was

placed over the middle well, with wrist and forearm Velcroed to the board. The subject then used the index finger to move a glass marble to successive target wells identified on a computer screen. Novel sequences of target wells were provided for each training session. A training session consisted of 4 trials, and at 100 targets/trial, thus, contained 400 targets. Subjects were instructed to complete two training sessions per day, and to keep the two sessions separated by >2 h. Subjects completed only one training session on TMS days, and thus a total of 20 sessions during the study. Compliance was monitored via e-mail and telephone contact. For each training session, time to complete each trial was recorded, averaged, and expressed as average time to complete one trial.

Data analysis

First-level MNT and TMS analyses were performed blinded to genotype data; note that TMS and behavioral data were also all collected blinded to genotype data. All analyses were performed with significance defined at threshold of $P < 0.05$.

Subjects

Demographic and behavioral data were examined between genotype groups using two-tailed t tests or Chi-square testing.

MNT performance

Short-term learning was defined as the change in time needed to complete a 100-target MNT trial from the first to the fourth trial during the MNT testing sessions on Day 1, on Day 5, and on Day 12. This was assessed using two-tailed paired t tests. Long-term learning was defined based on MNT performances across the 20 training sessions, using repeated measures ANOVA to examine the main effect of time and of genotype group as well as the time \times genotype interaction. For each training session,

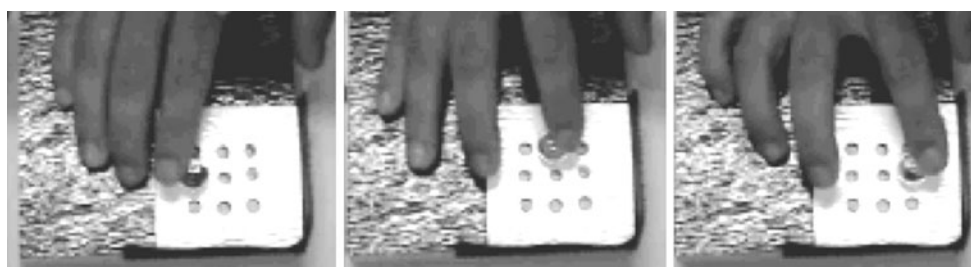


Fig. 1 Marble navigation task: on each day of the 12-day protocol, subjects guided a marble through a sequence of wells using the *right* index finger. This required extensive use of the *right* FDI, the same muscle for which representation was mapped during TMS sessions

time to complete a trial was also calculated as percent change from the first testing session.

TMS measures

Map area and map volume were calculated as described elsewhere (Kleim et al. 2006, 2007). For TMS data, peak-to-peak MEP amplitude was measured offline using Scope software (ADI; Colorado Springs, CO). MEP amplitude was averaged over the 10 stimulations acquired at each site, at each stimulation intensity. Short-term cortical motor map plasticity was assessed on Day 1, on Day 5, and on Day 12 by comparing TMS measures obtained before versus after the 30 min of FDI activity, and analyzed using paired *t* tests. These were two-tailed with one exception: because this short-term probe is known to increase, not decrease, map area (Kleim et al. 2006), one-tailed statistics were used for this measure. Long-term cortical motor map plasticity was assessed by comparing TMS data obtained prior to FDI simple activity on Day 1 with these data obtained on Day 12, then analyzed using repeated measures ANOVA. The primary TMS outcome measure was map area, which corresponds to activation measures found useful in prior fMRI studies of human motor system short-term plasticity (Karni et al. 1995; Floyer-Lea and Matthews 2005) and which has been a robust measure of motor cortex plasticity in prior TMS studies (Kleim et al. 2006), with secondary measures being map volume and MEP amplitudes at 4 levels (90, 110, 130, 150% LMT).

Results

Subjects

Demographic and behavioral measures (Table 1) did not differ between the two genotype groups. TMS data were obtained as planned with three exceptions, each due to subject unavailability, two on Day 5 and one on Day 12. All MNT data were collected as planned except that for one subject, MNT data could not be analyzed across the first 6 days.

Learning via MNT training

Subjects showed significant short-term and long-term learning with the MNT, which did not differ according to genotype. Regarding short-term learning, the change in MNT score across the four trials on Day 1 was significant across all subjects ($P < 0.05$) but did not differ according to BDNF genotype ($P > 0.4$). This was also true at Day 5. By Day 12, short-term learning was not significant. Regarding long-term learning (Fig. 2), significant learning

Table 1 Subject demographics and baseline behavior

	Val/Val subjects	Met carriers	<i>P</i>
<i>n</i>	12	12	
Age (years)	22.7 ± 1.2	21.2 ± 1.0	0.34
Gender (M/F)	6/6	6/6	1.00
Ethnicity			0.49
Asian	6	7	
White	5	4	
Hispanic	1	1	
Handedness	1.8 ± 0.07	1.8 ± 0.07	0.74
Pegboard (sec)	17.1 ± 0.6	18.3 ± 0.7	0.22
Finger tapping rate (Hz)	4.8 ± 0.4	4.6 ± 0.3	0.55
Pinch grip force (lbs)	19.8 ± 0.9	18.6 ± 1.5	0.53
Reaction time (msec)	30.2 ± 1.6	26.9 ± 1.7	0.17
CES depression score	7.0 ± 1.6	7.6 ± 1.0	0.75
STAI anxiety state score	29.3 ± 1.8	29.2 ± 1.7	0.99
STAI anxiety trait score	32.4 ± 1.9	34.7 ± 3.0	0.54
Digit span forwards	11.0 ± 0.6	11.5 ± 0.5	0.56
Digit span backwards	6.7 ± 0.5	8.2 ± 0.5	0.06
Marble board, time to complete 100 targets (sec)	479 ± 67	332 ± 25	0.047

Values are mean ± SEM. Handedness scores indicate subjects were strongly right handed (+2 = right handed, −2 = left handed). Marble board data were at baseline, at the first training session

was present over the first 18 training sessions (main effect of time, $P = 0.018$), with a plateau over the final two sessions. The time × genotype interaction was not significant ($P > 0.9$), however, suggesting that long-term learning also did not differ in relation to BDNF genotype.

Short-term plasticity

The TMS probe of short-term cortical motor map plasticity disclosed differences according to BDNF genotype on Day 1 (only Val/Val subjects showed short-term cortical motor map plasticity), but with subsequent intense MNT training, genotype-based differences in short-term cortical motor map plasticity were absent on Day 5 (short-term cortical motor map plasticity present in both groups) and on Day 12 (present in neither group).

On Day 1, at baseline, prior to the 30 min of simple FDI activity, there were no significant differences in any TMS measure according to genotype. On Day 1, across the 30 min of FDI activity used to probe short-term plasticity, repeated measures ANOVA across all subjects found no main effect of time on map area ($P > 0.23$; Fig. 3), but did reveal differential training effect on map area according to genotype (time × genotype interaction, $P = 0.016$). Thus, following 30 min of activity on Day 1, Val/Val subjects showed a significant increase in map area ($P = 0.01$),

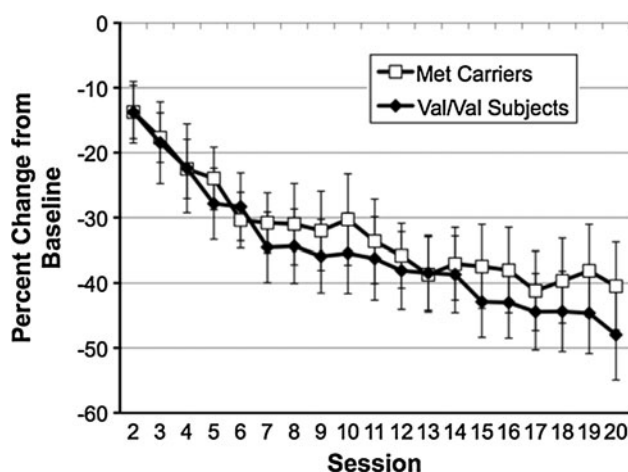


Fig. 2 Marble performance: percent change (relative to *baseline*) in time to complete a 100-target marble board trial (mean \pm SEM) is shown, for each training session. Motor learning over the 12 days did not vary according to genotype. Values are negative, because time to complete each trial decreases with training

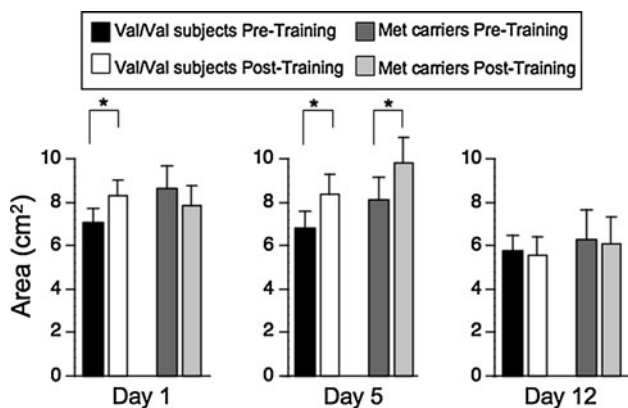


Fig. 3 Intense training overcomes effects of the val⁶⁶met BDNF polymorphism on short-term plasticity: The two genotype groups showed differences in short-term cortical motor map plasticity at *baseline*, but no differences in short-term plasticity were seen following 5 or 12 days of training. Thus, on Day 1, 30 min of simple right FDI activity produced a significant (* $P < 0.05$) increase in map area for Val/Val subjects but not for Met carriers. On Day 5 of intense training, however, both genotype groups showed increased map area across the 30 min of activity, and neither group showed increased map area across the 30 min of activity at Day 12 of intense training. Intense training overcomes effects of the val⁶⁶met BDNF polymorphism on short-term cortical motor map plasticity

while Met carriers did not ($P > 0.8$; Fig. 3). Among secondary TMS measures, the same time \times genotype effect was seen for map volume ($P = 0.032$) but not for the MEP amplitude measures.

On Day 5, there were again no differences between the two genotype groups on any TMS measure before the 30 min of simple FDI activity. Across the 30 min of activity, repeated measures ANOVA across all subjects found a significant ($P = 0.008$) effect of time on map area.

This change in map area did not vary by genotype (time \times genotype interaction, $P > 0.85$), as both the Val/Val subjects ($P < 0.05$) and the Met carriers ($P < 0.03$) showed a significant map area increase. Again, these changes were paralleled by map volume ($P = 0.011$, time \times genotype interaction) but not MEP amplitude measures.

On Day 12, there were again no differences between the two genotype groups on any TMS measure before the 30 min of activity. Across the 30 min of simple FDI activity, repeated measures ANOVA across all subjects found no significant main effect of time on map area ($P > 0.4$; Fig. 3). The time \times genotype interaction was also not significant ($P > 0.97$), and neither group showed map expansion following training ($P > 0.25$ for each). The same was true for the secondary TMS measures.

On each of the 3 days, short-term plasticity, measured across the 30 min of FDI simple activity, did not correlate significantly with short-term learning, measured as change in performance across that day's four MNT trials.

Long-term plasticity

Significant long-term cortical motor map plasticity was present and was similar in the two genotype groups. Across all subjects, from Day 1 to Day 12, the map area measured prior to the 30 min of simple FDI activity decreased significantly ($P = 0.02$, Fig. 4), as did the map volume ($P = 0.0087$) and MEP amplitudes at 110% ($P = 0.042$) and 130% ($P = 0.017$). None of these results varied significantly by genotype (time \times genotype interaction, $P > 0.05$).

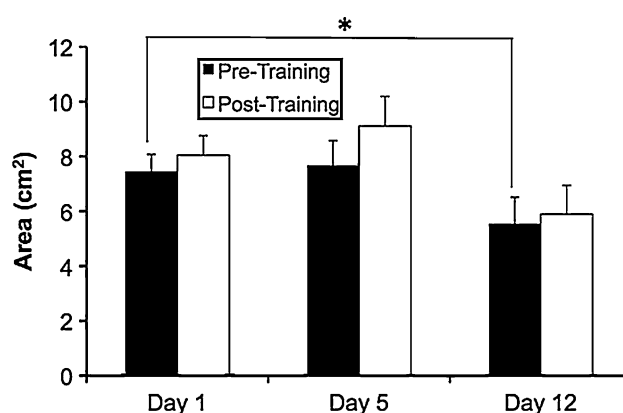


Fig. 4 Long-term cortical plasticity did not vary according to genotype: across all subjects, the TMS map area obtained prior to 30 min of simple activity contracted significantly (* $P < 0.05$) from Day 1 to Day 12. However, this long-term cortical motor map plasticity did not vary by genotype, as the time \times genotype interaction was not significant. Thus, significant long-term cortical plasticity was present, but this did not vary according to genotype

Long-term plasticity, measured as the change in map area from Days 1 to 12, did not correlate significantly with long-term learning, measured as change in MNT performance over the same time interval.

Discussion

The BDNF val⁶⁶met polymorphism impairs activity-dependent release of this growth factor, and accordingly has been associated with reduced short-term cortical plasticity. The current study aimed to determine whether intense training can overcome these polymorphism effects on short-term cortical motor map plasticity, and also to understand the effects of this polymorphism on long-term cortical motor map plasticity, given that long- and short-term plasticity have fundamental molecular differences (Costa et al. 2004). On Day 1, a probe of short-term cortical motor map plasticity demonstrated the expected genotype-related differences, with significant motor map enlargement across 30 min of simple activity in Val/Val subjects but not in Met carriers. Subjects then trained on the MNT for 12 days. At Day 5 of MNT training, a genotype-based difference in short-term plasticity was no longer found, as both genotype groups showed significant short-term cortical motor map plasticity across the 30 min of activity, suggesting that intense, sustained training overcame polymorphism effects on short-term cortical motor map plasticity. Also, long-term cortical motor map plasticity in relation to the 12 days of MNT training consisted of a significant reduction in map area, and this did not vary in relation to genotype, suggesting that polymorphism effects seen with short-term cortical plasticity are not found with long-term plasticity.

The current study confirms the previous finding that BDNF genotype influences short-term experience-dependent plasticity in the human motor cortex (Kleim et al. 2006), and suggests that sustained intense training can overcome this genotype effect. In the previous TMS study and on Day 1 of the current study, a significant time \times genotype interaction was seen across 30 min of FDI activity, with training-induced map enlargement in Val/Val subjects but not Met carriers (Fig. 3). These results have been corroborated using fMRI (McHughen et al. 2010), as well as using TMS across other probes of short-term plasticity (Cheeran et al. 2008). Importantly, the current study found that the genotype-based difference in short-term cortical motor map plasticity found on Day 1 was not present on Day 5 or on Day 12. Across 30 min of simple activity, short-term map plasticity on Days 5 and 12 of training no longer varied in relation to genotype (Fig. 3). There are several possible interpretations to explain how intense training might overcome the effects of the val⁶⁶met

polymorphism. Pre-synaptic events might play a role, as sustained training results in an up-regulation of BDNF gene expression (Berchtold et al. 2010; Neeper et al. 1995; Gomez-Pinilla et al. 2002), which results in a larger pool of readily-releasable BDNF protein. The current findings suggest that such a multi-day increase in BDNF expression could be enough to overcome the deficit in activity-dependent release associated with the val⁶⁶met polymorphism. This interpretation is further supported by studies of mice with impairments in BDNF trafficking and release, which showed that deficits in synaptic plasticity can be rescued by up-regulating BDNF levels (Simmons et al. 2009). An alternative interpretation is that the current findings reflect changes in post-synaptic events (Nagappan and Lu 2005) consequent to sustained training. Indeed, a number of conditions have been described that up-regulate post-synaptic trkB receptor expression (Pezet et al. 2002), which might augment synaptic plasticity and overcome effects of the val⁶⁶met polymorphism (Fritsch et al. 2010). The BDNF val⁶⁶met polymorphism is more common in non-Whites (Shimizu et al. 2004), and its behavioral effects may be less robust in this group (Bath and Lee 2006), suggesting that the current results might require further study using separate ethnic subgroups.

Long-term plasticity over 12 days of MNT training was significant, but it did not differ according to genotype (Fig. 4). Long-term plasticity consisted of a significant decrease from Day 1 to Day 12 in the TMS map area that was obtained prior to 30 min of FDI activity. The fact that this change did not differ in relation to BDNF genotype suggests that long-term cortical plasticity (map area contraction over 12 days) is not affected by the val⁶⁶met polymorphism in the same way as short-term plasticity (map area expansion over 30 min). One possible explanation for the lack of genotype effect on long-term cortical motor map plasticity is the increased levels of BDNF associated with sustained training (Berchtold et al. 2010; Neeper et al. 1995; Gomez-Pinilla et al. 2002), the extent of which parallels length of exposure to exercise (Neeper et al. 1995). Additionally, the impact of BDNF might be diluted with time, for example, angiogenesis (Kleim et al. 2002; Swain et al. 2003), astrocyte proliferation (Li et al. 2005), and synaptogenesis (Kleim et al. 2004) increase with long-term training and so might reduce the contribution of BDNF on long-term plasticity.

Behavioral learning with the MNT paradigm did not have a significant relationship with BDNF genotype, in either the short-term or long-term. This was somewhat surprising, as the val⁶⁶met polymorphism has been associated with reduced learning in a number of other learning paradigms, such as verbal episodic memory (Egan et al. 2003), a visual pinch force task (Fritsch et al. 2010), and a driving-based motor learning task (McHughen et al. 2010).

The reason that some learning paradigms vary according to BDNF genotype and some do not is not clear, but may be related to the content of training: BDNF genotype is related to traits such as anxiety (Hashimoto 2007) and memory (Egan et al. 2003), and traits such as these might have been of low relevance to MNT performance. Regardless, MNT training did affect motor cortex, as its use was associated with change in cortical motor map plasticity over 5 days (Met carriers came to demonstrate significant short-term plasticity) and over 12 days (significantly reduced map size), and serial TMS assessments in the absence of training do not show significant change (Pascual-Leone et al. 1995). One interpretation of these collective findings is that MNT training induces neuronal changes that are sufficient to overcome genotype effects on cortical motor map plasticity and leads to behavioral gains that do not vary by genotype. Behavioral learning with the MNT paradigm also did not correlate with the extent of concomitant cortical plasticity, for both short-term and long-term. On the one hand, this was unexpected, as the MNT paradigm and the 30 min of activity underlying the TMS probe of short-term cortical motor map plasticity each produce high demands on the right FDI. On the other hand, this is not surprising, as these were very different motor tasks: the 30 min of activity consisted of simple repetitive movements, while the MNT training was a complex fine motor task.

The current results suggest that sustained intense training can overcome the effects of the val⁶⁶met polymorphism on short-term cortical plasticity and describe a lack of polymorphism effect on long-term cortical plasticity. This might have broad therapeutic implications (Ji et al. 2010), given the role that decreased BDNF signaling appears to play in numerous neurological diseases (Siironen et al. 2007; Zuccato and Cattaneo 2009; Cramer et al. 2010), as well as psychiatric conditions and normal cognition (Rybakowski 2008). The current results suggest a framework for paradigms to modify the effect that BDNF genotype has on cortical plasticity.

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